Subjective Cognitive Decline: Mapping Functional and Structural Brain Changes—A Combined Resting-State Functional and Structural MR Imaging Study[1]

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Purpose: To determine whether individuals with subjective cognitive decline (SCD) exhibit functional and structural brain alterations by using resting-state functional and structural magnetic resonance (MR) imaging.

Materials and Methods: This study received institutional review board approval, and all participants gave informed consent. Resting-state functional MR imaging and structural MR imaging techniques were used to measure amplitude of low-frequency fluctuations (ALFF) and regional gray matter volume in 25 subjects with SCD (mean age, 65.52 years ± 6.12) and 61 control subjects (mean age, 64.11 years ± 8.59). Voxel-wise general linear model analyses were used to examine between-group differences in ALFF or in gray matter volume and to further determine the brain-behavioral relationship.

Results: Subjects with SCD exhibited higher ALFF values than did control subjects in the bilateral inferior parietal lobule (left: 0.44 ± 0.25 vs 0.27 ± 0.18, respectively; P = .0003; right: 1.46 ± 0.45 vs 1.10 ± 0.37, respectively; P = .0015), right inferior (0.45 ± 0.15 vs 0.37 ± 0.08, repectively; P = .0106) and middle (1.03 ± 0.32 vs 0.83 ± 0.20, respectively; P = .0008) occipital gyrus, right superior temporal gyrus (0.11 ± 0.07 vs 0.07 ± 0.04, respectively; P = .0016), and right cerebellum posterior lobe (0.51 ± 0.27 vs 0.39 ± 0.15, respectively; P = .0010). In the SCD group, significant correlations were found between Auditory Verbal Learning Test recognition scores and ALFF in the left inferior parietal lobe (r = −0.79, P < .001) and between Auditory Verbal Learning Test immediate recall scores and ALFF values in the right middle occipital gyrus (r = −0.64, P = .002). Nonsignificant group differences were found in gray matter volume (P > .05, corrected).

Conclusion: Individuals with SCD had altered spontaneous functional activity, suggesting that resting-state functional MR imaging may be a noninvasive method for characterizing SCD.

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Individuals with subjective cognitive decline (SCD) are elderly people who self-report persistent decline in cognitive capacity without measurable cognitive impairment according to results of standard assessments (1). Increasing evidence has suggested that individuals with SCD exhibit a trend toward a greater risk of cognitive decline and the development of mild cognitive impairment and Alzheimer disease (AD) (1). Therefore, SCD may serve as a clinical indicator for early detection of AD (2) and may arouse growing research interests.

Authors of previous brain imaging studies have documented structural and functional changes in individuals with SCD. For example, several structural magnetic resonance (MR) imaging studies showed that subjects with SCD have a loss of gray matter (GM) volume and/or concentration (the proportion of GM relative to other tissues in a region) in the hippocampus (3,4), entorhinal cortex (5), and frontotemporal regions (4). However, there are a few studies in which authors showed an absence of GM loss in patients with SCD (6,7). By using task-based functional MR imaging, Rodda and colleagues (8) reported that subjects with SCD exhibited higher functional activation in the left medial temporal, occipitoparietal, and medial frontal cortex during a verbal episodic memory encoding task compared with control subjects. In another task-based functional MR imaging study, they further proved that subjects with SCD exhibited higher activation in the left medial temporal lobe, bilateral thalamus, and posterior cingulate during a divided-attention task (9). Such patterns are largely consistent with decreased activation previously shown in patients with AD, suggesting a potential compensatory mechanism in subjects with SCD (9). These findings based on brain imaging techniques provided insights into the pathophysiologic mechanisms of SCD. Despite these advances, the previously mentioned studies were mainly focused on single-modality imaging data, providing limited information about the potential brain alterations in subjects with SCD. To our knowledge, authors of few studies have reported both structural and functional brain changes in the same SCD group by using multimodal imaging techniques.

In this study, we used resting-state functional MR imaging and structural MR imaging techniques to examine patterns of regional spontaneous brain activity and GM morphology in subjects with SCD and healthy control subjects. Resting-state functional MR imaging does not require specific task paradigms and can allow noninvasive measurement of spontaneous or intrinsic brain activity. The amplitude of low-frequency fluctuations (ALFF) was chosen as a resting-state functional MR imaging index that can capture regional intensity of spontaneous fluctuations in blood oxygenation level–dependent signals (10) and reflect the regional metabolic level of glucose (11). Resting-state functional MR imaging ALFF has been applied to study functional abnormalities of AD (12) and amnestic mild cognitive impairment (13); however, the finding of spontaneous functional brain changes in patients with SCD has not been well established in the literature. In addition, in this study, voxel-based morphologic analysis was performed to detect loss of GM volume, which provides complementary information of brain changes in patients with SCD. On the basis of previous task-based functional MR imaging and structural MR imaging studies in patients with SCD (8,9), we hypothesized that there is higher spontaneous brain activity and more GM alterations in individuals with SCD compared with those in control subjects. The purpose of this study was to determine whether individuals with

Advances in Knowledge

- Compared with control subjects, individuals with subjective cognitive decline (SCD) showed higher amplitude of low-frequency fluctuations (ALFF) in the bilateral inferior parietal lobule, right inferior and middle occipital gyri, right superior temporal gyrus, and right cerebellum posterior lobe; there were no significant differences in gray matter volume between the groups ($P > .05$, corrected).
- In the SCD group, significant correlations were found between auditory verbal learning test score (immediate recall) and ALFF values in the right middle occipital gyrus ($r = -0.636$, $P = .002$) and between auditory-verbal learning test scores (recognition) and ALFF values in the left inferior parietal lobe ($r = -0.788$, $P < .001$).

Implication for Patient Care

- Higher intrinsic or spontaneous brain activity measured by means of resting-state functional MR imaging was observed in individuals with subjective cognitive decline, indicating that there might be a compensatory mechanism in the early stage of Alzheimer disease and that resting-state functional MR imaging is an important technique for detecting brain alterations in individuals with subjective cognitive decline.

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Abbreviations:
AD = Alzheimer disease
ALFF = amplitude of low-frequency fluctuations
AVLT = Auditory Verbal Learning Test
GM = gray matter
SCD = subjective cognitive decline

Author contributions:
Guarantors of integrity of entire study, Y.S., Y. Han; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, Y.S., Z.J.D., C.S., X.N.W., Y. He; clinical studies, Y.S., Y.X.L., C.S., H.Y.L., X.N.W., Y. Han; experimental studies, Y.S., Z.J.D., Y. He, Y. Han; statistical analysis, Y.S., Z.J.D., X.D.C., Y. He; and manuscript editing, Y.S., Z.J.D., Y.X.L., C.S., X.N.W., Y. He, Y. Han

Conflicts of interest are listed at the end of this article.

SCD exhibit functional and structural brain alterations.

Materials and Methods

Participants

A total of 269 right-handed subjects were enrolled from May 2011 to June 2014. Among them, 208 individuals with memory concerns including AD, mild cognitive impairment, and SCD were recruited from the memory clinic of the Neurology Department of Xuan-Wu Hospital in Beijing, China, and 61 healthy control subjects were recruited from the local community by means of advertisement. A standardized clinical evaluation protocol was used, including a medical history interview, neurologic examination, and a battery of neuropsychological tests for all subjects. The neuropsychological tests, which included the Chinese version of the Mini–Mental State Examination (14), the Beijing version of Montreal Cognitive Assessment (15), clinical dementia rating, the auditory verbal learning test (AVLT [16]), Hachinski ischemic scale, Hamilton depression rating scale (17), the Center for Epidemiologic Studies depression scale (18), and Activities of daily living scale were performed by two authors (C.S. and Y.S., with 3 and 2 years of experience, respectively).

The inclusion criteria for SCD (based on the research criteria for pre-mild cognitive impairment SCD [1]) were as follows: *(a)* self-reported experience of persistent decline in memory compared with a previous state (within the past 5 years), which was further confirmed further by informants; *(b)* scores on both the Mini–Mental State Examination and the Montreal Cognitive Assessment that were within the normal range (adjusted for age, sex, and education); *(c)* a Clinical Dementia Rating score of 0. The healthy control subjects were volunteers without cognitive decline concerns and whose neuropsychological tests scores were in normal range. Subjects were excluded if they had any of the following: *(a)* history of stroke, *(b)* depression, *(c)* another central nervous system disease that causes cognitive decline (eg, brain tumor, Parkinson disease, encephalitis or epilepsy), *(d)* other diseases that cause cognitive decline (eg, thyroid dysfunction, severe anemia, syphilis, or HIV), *(e)* history of psychosis or congenital mental growth retardation, or *(f)* traumatic brain injury. The diagnosis was performed by experienced neurologists (Y.Han, H.Y.L., and Y.X.L., with 28, 12, and 8 years of experience, respectively). Details of the enrollment process are shown in a flowchart of the study (Fig 1). After collecting the data of all the subjects, we followed up the SCD and control subjects from June 2014 to December 2015. None of the subjects with SCD showed progression to mild cognitive impairment or AD, and the control subjects did not show progression to SCD during this time.

Figure 1

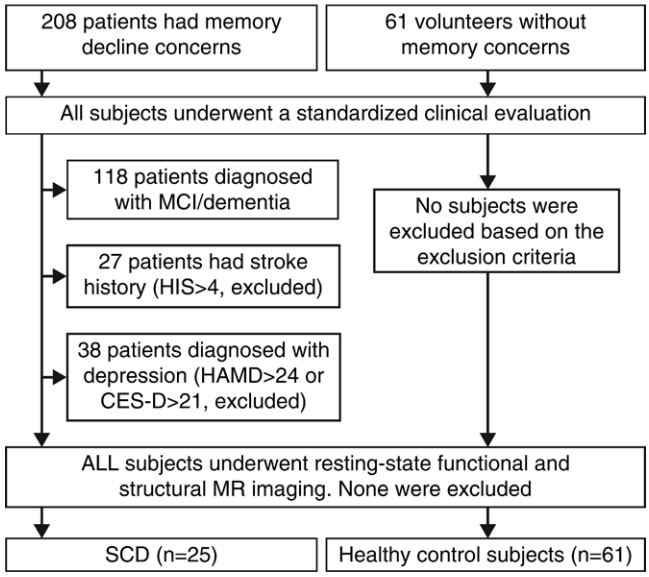

Figure 1: Flowchart shows selection of subjects. *MCI* = mild cognitive impairment, *CDR* = Clinical Dementia Rating, *HIS* = Hachinski Ischemic Scale, *HAMD* = Hamilton depression rating scale, *CES-D* = Center for Epidemiologic Studies Depression Scale.

Data Acquisition

All of the participants were imaged with a 3-T MR imager (Magnetom Sonata; Siemens, Erlangen, Germany). Foam pads and headphones were used to minimize head movement and imager noise. Functional images were collected axially by using an echo-planar imaging sequence: repetition time msec/echo time msec, 2000/40; flip angle, 90°; field of view, 240 × 240 mm^2; matrix, 64 × 64; number of sections, 28; section thickness, 4 mm; voxel size, 3.75 × 3.75 × 4 mm^3; gap, 1 mm; and bandwidth, 2232 Hz per pixel. Before undergoing imaging, the subjects were instructed to keep their eyes closed but not fall asleep, to relax their minds, and to move as little as possible during imaging. The sequence lasted for 478 seconds and thus included 239 functional volumes for each subject. Three-dimensional T1-weighted magnetization-prepared rapid gradient-echo sagittal images also were obtained by using the following sequence: 1900/2.2; flip angle, 9°; inversion time, 900 msec; field of view, 256 × 256 mm^2; matrix, 256 × 256; number of sections, 176; section thickness, 1 mm; and voxel size, 1 × 1 × 1 mm^3.

Data Preprocessing

All data were processed by one author (Z.J.D., with 6 years of experience in both resting-state functional MR

imaging and structural MR imaging). Image preprocessing was performed by using software (Statistical Parametric Mapping [*http://www.fil.ion.ucl.ac.uk/spm*] and Data Processing Assistant for Resting-State Functional MR Imaging [DPARSF] [19]). For imager stabilization and to allow the participants to adapt to the environment, the first 10 volumes were discarded. The remaining functional sequences were first corrected for timing differences and motion effects. None of the subjects were excluded on the basis of the criterion of more than 3 mm of translation or 3° of rotation in any direction. Next, the individual structural images (T1-weighted magnetization-prepared rapid gradient-echo images) were coregistered to the mean functional image after motion correction by using a linear transformation (20). The transformed structural images were then segmented into GM, white matter, and cerebrospinal fluid by using a unified segmentation algorithm (21). The motion-corrected functional volumes were spatially normalized to Montreal Neurologic Institute space and resampled to 3-mm isotropic voxels by using the normalization parameters estimated during unified segmentation. After a linear trend of the time course was removed, a band-pass filter (0.01–0.08 Hz) was applied. Finally, nuisance signals (including Friston 24-head motion parameters [22], the mean global signal, and the white matter and cerebrospinal fluid signals) were extracted and regressed out from the data to reduce the effects of nonneuronal signals. The resultant residual time series were used for further analyses. Given that the removal of global brain signal may discard the information of baseline neuronal activity (23), we reanalyzed the resting-state functional MR imaging data without removing the mean global signal.

Functional ALFF Analyses

To measure regional spontaneous brain activity, we computed the ALFF (10) in a voxel-wise manner. For a given voxel, the residual time series was first converted to the frequency domain by using a fast-Fourier transform. The square root of the power spectrum was computed and then averaged throughout 0.01–0.08 Hz. This averaged square root was defined as the ALFF. For each subject, we obtained an individual ALFF map, which was further spatially smoothed with a Gaussian kernel (full width at half maximum, 4 mm). These procedures were performed with a resting-state functional MR imaging data-analysis toolkit (REST, *http://rest.restfmri.net*) (24).

Structural Voxel-based Morphometric Analyses

To determine the spatial pattern of GM loss in patients with SCD, we performed a voxel-based morphometric analysis of the structural images (25). Jacobian modulation was applied to the segmented GM images in the Montreal Neurologic Institute space, which were obtained by using the unified segmentation algorithm as described previously. After this, a spatial smoothing procedure with a Gaussian kernel (full width at half maximum, 10 mm) was performed on the modulated GM images. Finally, for each subject, we obtained a smoothed GM volumetric map.

Statistical Analyses

We used two-sample two-tailed t tests to detect the group differences between patients with SCD and control subjects in age, education level, and neuropsychological tests scores, and we used a two-tailed Pearson χ^2 test to compare group differences in sex.

To examine between-group differences in either ALFF or GM volume, a voxel-wise general linear model analysis was performed with age, sex, and education level as covariates. The complete general linear model was formulated as:

$$Y = \beta_0 + \beta_1 \times V_{group} + \beta_2 \times V_{age} + \beta_3 \times V_{sex} + \beta_4 \times V_{edu},$$

where Y is a dependent variable (ALFF or GM volume), V_{group} is the difference in values between groups, V_{age} is the difference in age, V_{sex} is the difference in values between the sexes, V_{edu} is the difference in values for education level, and β_0–β_4 are parameters that must be estimated. The statistical significance threshold was set at a height threshold P value of less than .05 and cluster size greater than 2160 mm^3 for the ALFF analyses and a height threshold P value of less than .05 and a cluster size greater than 8360 mm^3 for the GM volume analyses, both of which corresponded to a corrected P value of less than .05. These statistical analyses were confined within the GM mask (size: 1588923 mm^3) that was generated by thresholding (a threshold of 0.2) of the mean GM probability map of all of the subjects. Corrections for multiple comparisons were performed with Monte Carlo simulations (26) by using the AFNI AlphaSim program (*http://afni.nimh.nih.gov/pub/dist/doc/manual/AlphaSim.pdf*).

To determine the relationships between ALFF (or GM volume) and verbal episodic memory performance (AVLT-immediate recall, AVLT-delayed recall, and AVLT-recognition), a voxel-based general linear model analysis was conducted in the SCD group within the regions showing significant group differences in ALFF (or GM volume), with age, sex, and education level as covariates. Multiple comparisons were again corrected byusing Monte Carlo simulations.

Results

The present study included 25 subjects with SCD (mean age, 65.52 years ± 6.12) and 61 healthy control subjects (mean age, 64.11 years ± 8.59). Table 1 summarizes the participants' demographic characteristics and neuropsychological test results. No significant differences were found ($P > 0.1$ for all) in age, sex, education level, and Mini–Mental State Examination and Montreal Cognitive Assessment scores between the SCD and control subjects. There were significant group differences in AVLT-immediate recall, AVLT-delayed recall and AVLT-recognition (all, $P < 0.004$).

Individuals in the SCD group had higher ALFF values than did those in the control group in the bilateral inferior parietal lobule (left: 0.44 ± 0.25

Table 1

Demographic and Neuropsychological Tests of SCD and Healthy Control Groups

Demographics and Tests	Patients with SCD (n = 25)	Control Subjects (n = 61)	P Value
Age (y)	65.52 ± 6.12	64.11 ± 8.59	.460
Sex*			.907
Male	14	35	
Female	11	26	
Education	10.64 ± 4.10	11.30 ± 4.90	.557
Mini–Mental State Examination scores	27.68 ± 1.49	28.33 ± 2.09	.163
Montreal Cognitive Assessment scores	26.36 ± 2.29	26.67 ± 2.69	.612
AVLT, immediate recall scores	7.52 ± 1.78	9.41 ± 1.71	<.001
AVLT, delayed recall scores	7.76 ± 1.83	10.33 ± 2.80	<.001
AVLT, recognition scores	10.60 ± 1.96	12.16 ± 2.30	.004

Note.—Unless otherwise indicated, data are presented as means ± standard deviation.

* Data are number of patients.

vs 0.27 ± 0.18, respectively; P = .0003; right: 1.46 ± 0.45 vs 1.10 ± 0.37, respectively; P = .0015), right inferior occipital gyrus (0.45 ± 0.15 vs 0.37 ± 0.08, respectively; P = .0106), right middle occipital gyrus (1.03 ± 0.32 vs 0.83 ± 0.20, respectively; P = .0008), right superior temporal gyrus (0.11 ± 0.07 vs 0.07 ± 0.04, respectively; P = .0016), and right cerebellum posterior lobe (0.51 ± 0.27 vs 0.39 ± 0.15, respectively; P = .0010) (Fig 2, Table 2). No lower ALFF was detected for the SCD group compared with control subject group. When we omitted the global signal regression in the preprocessing of resting-state functional MR imaging data, we found that all of the results were preserved except for those in the right superior temporal gyrus (Fig E1 [online]). There were no significant differences between the groups in GM volume after correction for multiple comparisons. In the SCD group, there were significant negative correlations between AVLT-recognition and ALFF values of the left inferior parietal lobule (r = −0.788, P < .001, corrected) and between AVLT-immediate recall and ALFF values in the right middle occipital gyrus (r = −0.636, P = .002, corrected) (Fig 3).

Discussion

These current results suggest that, compared with control subjects, subjects with SCD present with many regions of altered brain function but not structure. Subjects with SCD had higher ALFF values primarily in the bilateral inferior parietal lobule, right middle occipital gyrus, right inferior occipital gyrus, right superior temporal gyri, and right posterior lobe of the cerebellum, whereas there was no significant difference between groups in GM volume. Moreover, the alterations of ALFF in the left inferior parietal lobule and right middle occipital gyrus of the SCD group significantly correlated with verbal episodic memory scores. By using resting-state functional MR imaging, we observed higher spontaneous brain activity in individuals with SCD, indicating a possible compensatory mechanism in the early stage of AD. Also, our study results indicate that resting-state functional MR imaging is an important technique for detecting brain alterations in patients with SCD.

The bilateral inferior parietal lobular regions are known as the major sites in the default-mode network and have been found to exhibit a breakdown of functional connectivity in patients with AD (27). Previous resting-state functional MR imaging studies have shown higher ALFF values in the left inferior parietal lobule of amnestic subjects with mild cognitive impairment (28) and lower ALFF values in the inferior parietal lobule of patients with AD (29) compared with control subjects. Thus, we speculate that the inferior parietal lobule may exhibit dynamic changes in spontaneous activity during the progression of AD, and the findings of higher inferior parietal lobule ALFF values in patients with SCD may indicate a compensatory mechanism in the early stage of this disease. In addition, higher ALFF values also were found in the middle occipital gyrus, inferior occipital gyrus, superior temporal gyri, and cerebellum in the SCD group. Abnormal spontaneous brain activity in these regions has been reported previously when amnestic subjects with mild cognitive impairment were compared with control subjects (13,30). Our findings suggest that the regions showing SCD-related changes in ALFF also were related to those exhibiting functional disruptions in patients with AD and/or mild cognitive impairment. Thus, we speculate that, throughout the course of AD progression, alterations in spontaneous brain activity in these regions may represent a compensatory mechanism in individuals with SCD.

Although functional alterations were present in patients with SCD, we did not observe significant group differences in GM volume. The finding of structural MR imaging was largely consistent with the results of previous studies (6,7). One possible explanation for these results is that neuronal dysfunction may precede neuronal atrophy and death in the progression of AD, according to the model of the temporal ordering of AD abnormalities (31). By combining structural MR imaging and positron emission tomography (PET), authors of a previous study of AD provided empirical support that hypometabolism largely exceeds GM atrophy in several brain regions (32). Our results of combined resting-state functional MR imaging and structural MR imaging provide further support the idea that functional alterations might occur before structural atrophy in patients with SCD. Collectively, these works raise the possibility that, compared with structural MR imaging that captures GM morphometry, resting-state functional MR imaging might be a more sensitive imaging technique for detecting brain

Figure 2

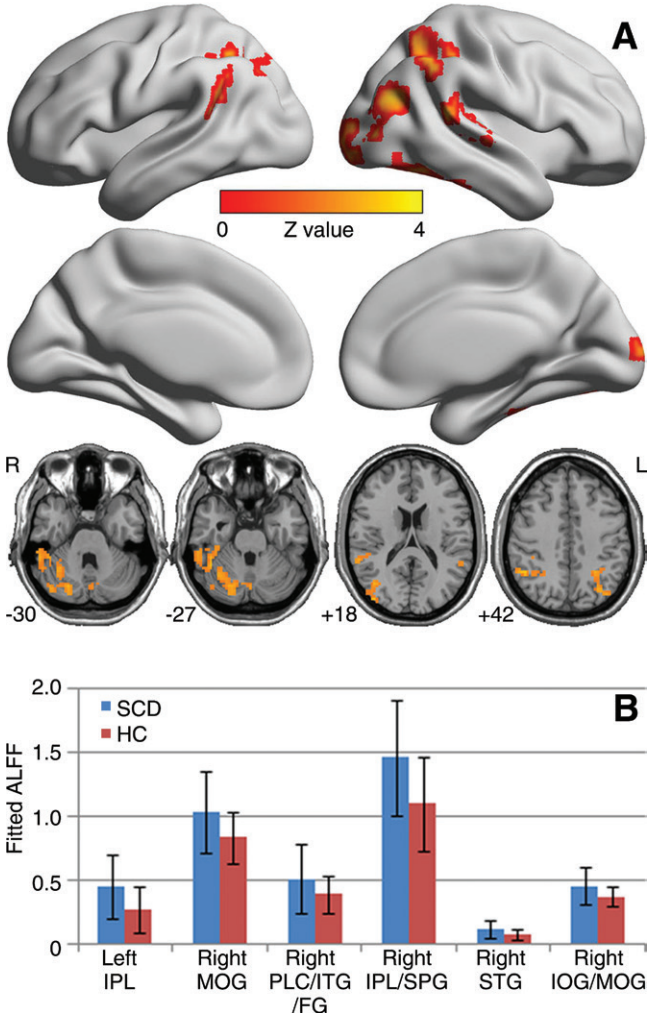

Figure 2: *A*, *Z*-value statistical difference maps in ALFF values between SCD (top two images on left) and healthy control subject (top two images on right). *Z* -value cortical surfaces were mapped by using the BrainNet Viewer *(http://www.nitrc.org/projects/bnv/)* (35). *B*, Bar graphs demonstrate fitted ALFF values at the peak voxel showing ALFF differences between groups. *FG* = fusiform gyrus, *IOG* = inferior occipital gyrus, *IPL* = inferior parietal lobule, *ITG* = inferior temporal gyrus, *MOG* = middle occipital gyrus, *PLC* = posterior lobe of the cerebellum, *SPG* = superior parietal gyrus, *STG* = superior temporal gyrus.

alterations in patients with preclinical AD. Nonetheless, results of structural MR imaging studies have been inconsistent, with some authors (3–5) finding loss of GM volume in individuals with SCD. The inconsistencies among these structural MR imaging studies could have occurred because SCD is an inchoate and long period in the progression of disease and authors of different studies may have collected the data with different SCD stages. On the other hand, the nonsignificant results may have been limited by the small sample size. Therefore, it would be important to recruit more participants with SCD to validate these results in the future.

In the current study, although we observed significant differences between groups in AVLT-immediate recall, AVLT-delayed recall and AVLT-recognition scores, the performance of subjects with SCD on the AVLT was still within the age-adjusted normal range (16). This finding was compatible with the notion that subtle cognitive deficits may be present in subjects with SCD (33). These indicate that individuals with SCD may adopt compensatory strategies that involve increased functional activity in several brain regions to maintain the normal performance in verbal episodic memory in the early stage of disease. However, the specific neural basis of this mechanism is still poorly understood. A possible explanation for this observation is that the neural compensation initiates the first attempts to maintain the impaired neural reserve and then recruits alternate neural networks to improve function (34). Consistent with the speculation, we found significant negative correlations between AVLT-recognition and regional ALFF values in the left inferior parietal lobule and between AVLT-immediate recall and regional ALFF values in the right middle occipital gyrus.

Our study had several limitations. First, the results were limited by the small sample size. Considering that our data were from an ongoing research project, further analyses with more participants with SCD should be conducted. Second, we did not include information on the biomarkers of AD (such as amyloid deposition) for the subjects with SCD. Thus, we could not determine if the symptoms of SCD were related to AD. Future studies that combine PET with multimodal MR imaging techniques would be important to elucidate the pathophysiologic mechanisms of the functional alterations in patients with SCD. Third, in this study we only collected data on verbal episodic memory performance for subjects with SCD. It would be important to include more cognitive tests (eg, executive function) to fully evaluate the brain-behavioral relationship in patients with SCD. Finally, the present study was cross-sectional. A longitudinal design would be very helpful to determine whether the profiles of increased functional activity identified in

Table 2

Regions Showing Significant ALFF Differences between the SCD and Control Groups

Brain Regions	Brodmann Area*	Volume (mm^3)	MNI Coordinates (mm) x	y	z	Fitted ALFF value, SCD†	Fitted ALFF Value, Control Subjects‡	*Z*-score
Left inferior parietal lobule	7/40	5508	−33	−72	48	0.44 ± 0.25	0.27 ± 0.18	3.587
Right middle occipital gyrus	19/39	4266	42	−72	24	1.03 ± 0.32	0.83 ± 0.20	3.333
Right posterior lobe of cerebellum, inferior temporal gyrus, and fusiform gyrus	37	13878	0	−72	−45	0.51 ± 0.27	0.39 ± 0.15	3.291
Right inferior pariental lobule, and superior parietal gyrus	40/7	4401	39	−51	54	1.46 ± 0.45	1.10 ± 0.37	3.172
Right superior temporal gyrus	41	2700	45	−30	6	0.11 ± 0.07	0.07 ± 0.04	3.159
Right inferior occipital gyrus and middle occipital gyrus	18	2457	24	−102	3	0.45 ± 0.15	0.37 ± 0.08	2.556

* The numbers in the Brodmann Area column indicate the corresponding Brodmann sub-areas. MNI = Montreal Neurologic Institute.

† Fitted ALFF value for SCD = mean ± standard deviation of fitted ALFF value in SCD group of peak voxel showing ALFF differences between the two groups.

‡ Fitted ALFF value for healthy control subjects = mean ± standard deviation of fitted ALFF value in healthy control group of peak voxel showing ALFF differences between the two groups.

§ *Z*-score = statistical value of peak voxel showing ALFF differences between the two groups

Figure 3

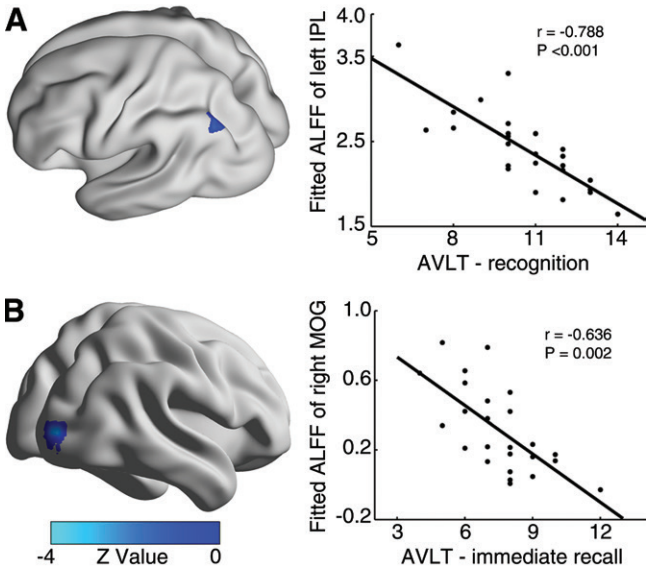

Figure 3: Relationships between cognitive performance and ALFF values in the SCD group. *A*, Brain surface map shows relationship of AVLT-recognition scores and ALFF. Scatterplot shows correlation between ALFF value of left inferior parietal lobule *(IPL)* and AVLT-recognition scores. *B*, Brain surface map shows correlations between AVLT-immediate recall and ALFFs in middle occipital gyrus *(MOG)* in patient with SCD. Scatterplot shows correlation between ALFF value of the right middle occipital gyrus and AVLT-immediate recall scores.

the individuals with SCD could be used to predict the development of objective memory decline and whether they are related to the subsequent risk for decline and dementia status.

In summary, although individuals with SCD did not show GM loss in our study, they showed functional alterations of spontaneous or intrinsic brain activity, and these alterations were correlated with episodic memory performance. These results suggest that resting-state functional MR imaging is a sensitive imaging technique for capturing brain alterations in individuals with SCD.

Disclosures of Conflicts of Interest: Y.S. disclosed no relevant relationships. **Z.J.D.** disclosed no relevant relationships. **Y.X.L.** disclosed no relevant relationships. **C.S.** disclosed no relevant relationships. **H.Y.L.** disclosed no relevant relationships. **X.N.W.** disclosed no relevant relationships. **X.D.C.** disclosed no relevant relationships. **Y.He** disclosed no relevant relationships. **Y.Han.** disclosed no relevant relationships.

References

1. Jessen F, Amariglio RE, van Boxtel M, et al. A conceptual framework for research on subjective cognitive decline in preclinical Alzheimer's disease. Alzheimers Dement 2014;10(6):844–852.

2. van Oijen M, de Jong FJ, Hofman A, Koudstaal PJ, Breteler MMB. Subjective memory complaints, education, and risk of Alzheimer's disease. Alzheimers Dement 2007; 3(2):92–97.

3. van der Flier WM, van Buchem MA, Weverling-Rijnsburger AW, et al. Memory complaints in patients with normal cognition are associated with smaller hippocampal volumes. J Neurol 2004;251(6):671–675.

4. Saykin AJ, Wishart HA, Rabin LA, et al. Older adults with cognitive complaints show brain atrophy similar to that of amnestic MCI. Neurology 2006;67(5):834–842.

5. Jessen F, Feyen L, Freymann K, et al. Volume reduction of the entorhinal cortex in subjective memory impairment. Neurobiol Aging 2006;27(12):1751–1756.

6. Selnes P, Fjell AM, Gjerstad L, et al. White matter imaging changes in subjective and mild cognitive impairment. Alzheimers Dement 2012;8(5 Suppl):S112–S121.

7. Wang Y, West JD, Flashman LA, et al. Selective changes in white matter integrity in MCI and older adults with cognitive complaints. Biochim Biophys Acta 2012;1822(3):423–430.

8. Rodda JE, Dannhauser TM, Cutinha DJ, Shergill SS, Walker Z. Subjective cognitive impairment: increased prefrontal cortex activation compared to controls during an encoding task. Int J Geriatr Psychiatry 2009;24(8):865–874.

9. Rodda J, Dannhauser T, Cutinha DJ, Shergill SS, Walker Z. Subjective cognitive impairment: functional MRI during a divided attention task. Eur Psychiatry 2011;26(7):457–462.

10. Zang YF, He Y, Zhu CZ, et al. Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI. Brain Dev 2007;29(2):83–91.

11. Tomasi D, Wang GJ, Volkow ND. Energetic cost of brain functional connectivity. Proc Natl Acad Sci U S A 2013;110(33):13642–13647.

12. Sheline YI, Raichle ME. Resting state functional connectivity in preclinical Alzheimer's disease. Biol Psychiatry 2013;74(5):340–347.

13. Han Y, Wang J, Zhao Z, et al. Frequency-dependent changes in the amplitude of low-frequency fluctuations in amnestic mild cognitive impairment: a resting-state fMRI study. Neuroimage 2011;55(1):287–295.

14. Jia J, Ning Y, Zhang J, Xu J, Wei W, Chen X. The recommendation of diagnosis and treatment of cognitive impairment in Chinese elderly. Chin J Geriatr 2014;33(8):817–825.

15. Lu J, Li D, Li F, et al. Montreal cognitive assessment in detecting cognitive impairment in Chinese elderly individuals: a population-based study. J Geriatr Psychiatry Neurol 2011;24(4):184–190.

16. Guo Q, Sun Y, Yu P, Zhen H, Lv C. Norm of Auditory Verbal Learning Test in the Normal Aged in China Community [in Chinese]. Chin J Clin Psychol 2007;15(2):132–134.

17. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62.

18. Dozeman E, van Schaik DJ, van Marwijk HW, Stek ML, van der Horst HE, Beekman AT. The center for epidemiological studies depression scale (CES-D) is an adequate screening instrument for depressive and anxiety disorders in a very old population living in residential homes. Int J Geriatr Psychiatry 2011;26(3):239–246.

19. Yan CG, Zang YF. DPARSF: A MATLAB toolbox for "pipeline" data analysis of resting-state fMRI. Front Syst Neurosci 2010;4:13.

20. Collignon A, Maes F, Delaere D, Vandermeulen D, Suetens P, Marchal G. Automated multi-modality image registration based on information theory. In: Bizais Y, Barillot C, Di Paola R, eds. Information processing in medical imaging. Dordrecht, the Netherlands: Kluwer, 1995;263–274.

21. Ashburner J, Friston KJ. Unified segmentation. Neuroimage 2005;26(3):839–851.

22. Friston KJ, Williams S, Howard R, Frackowiak RS, Turner R. Movement-related effects in fMRI time-series. Magn Reson Med 1996;35(3):346–355.

23. Schölvinck ML, Maier A, Ye FQ, Duyn JH, Leopold DA. Neural basis of global resting-state fMRI activity. Proc Natl Acad Sci U S A 2010;107(22):10238–10243.

24. Song XW, Dong ZY, Long XY, et al. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 2011;6(9):e25031.

25. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000; 11(6 Pt 1):805–821.

26. Ledberg A, Akerman S, Roland PE. Estimation of the probabilities of 3D clusters in functional brain images. Neuroimage 1998;8(2):113–128.

27. Buckner RL, Sepulcre J, Talukdar T, et al. Cortical hubs revealed by intrinsic functional connectivity: mapping, assessment of stability, and relation to Alzheimer's disease. J Neurosci 2009;29(6):1860–1873.

28. Xi Q, Zhao X, Wang P, et al. Spontaneous brain activity in mild cognitive impairment revealed by amplitude of low-frequency fluctuation analysis: a resting-state fMRI study. Radiol Med (Torino) 2012;117(5):865–871.

29. Liu X, Wang S, Zhang X, Wang Z, Tian X, He Y. Abnormal amplitude of low-frequency fluctuations of intrinsic brain activity in Alzheimer's disease. J Alzheimers Dis 2014; 40(2):387–397.

30. Yin C, Yi L, Jia L, et al. Early morphological brain abnormalities in patients with amnestic mild cognitive impairment. Transl Neurosci 2014;5(4):253–259.

31. Jack CR Jr, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12(2):207–216.

32. Chételat G, Desgranges B, Landeau B, et al. Direct voxel-based comparison between grey matter hypometabolism and atrophy in Alzheimer's disease. Brain 2008;131(Pt 1): 60–71.

33. Jessen F, Wiese B, Cvetanovska G, et al. Patterns of subjective memory impairment in the elderly: association with memory performance. Psychol Med 2007;37(12):1753–1762.

34. Steffener J, Stern Y. Exploring the neural basis of cognitive reserve in aging. Biochim Biophys Acta 2012;1822(3):467–473.

35. Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. PLoS One 2013;8(7):e68910.